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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/391,861	THOMASON ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-12,41-43 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12,41-43 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 23, 2007 that includes a response to the final office action dated June 27, 2006, has been entered. Claims 1-5, 7-12, 41-43 and 55 are pending in the application. Claims 39, and 49-54 have been cancelled. Claims 1, 2, 5 and 42 have been amended and claim 55 is newly added. Claims 1-5, 7-12, 41-43 and 55 are under current examination.

Applicants should note that the examiner of record has changed (see the last page of this office action). Applicants should further note that the introduction of new claim 55, directed to SEQ ID NOS: 5 and 6, not previously presented or examined, delays prosecution and presents an impediment to compact prosecution.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response & New Claim Objections

Claims 13 and 49-54 were objected for failure to comply with 37 CFR 1.121(c), in the previous office action dated June 27, 2006. In view of Applicants' claim amendments, deleting the text of cancelled claim 13 and identifying the claims with a correct status identifier, and cancellation of claims 49-54, the previous objections are hereby withdrawn.

Claims 5, 7, 42, 43, 53, and 54 were objected to under 37 CFR 1.75(c) as being in improper form, in the previous office action dated June 27, 2006. The cancellation of claims 53 and 54 renders their objections moot. In view of Applicants' claim amendments, removing the multiple dependencies of the remaining claims, the previous objection is hereby withdrawn.

Claim 1 is newly objected 2, because the claim recites: "either SEQ ID NO: 2 or SEQ ID NO: 4". The strikethrough of "4" appears to be in error. Appropriate correction is required.

Response & New Claim Rejections - 35 USC § 10-Utility & 35 USC § 112, first paragraph-Enablement

Claims 1-6, 7-13, 39, 41-43 and 49-52 stand rejected under 35 U.S.C. 101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The cancellation of claims 6, 13, 39 and 49-52 renders their rejections moot. The rejection set forth in the Office action of June 27, 2006 is maintained for claims 1-5, 7-12, and 41-43, and is further applied to newly added claim 55 for the reasons of record.

Claims 1-6, 7-13, 39, 41-43 and 49-52 stand rejected under 35 U.S.C. 112, first paragraph, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility and thus, one skilled in the art clearly would not know how to use the claimed invention. The cancellation of claims 6, 13, 39 and 49-52 renders their rejections moot. The rejection set forth in the Office action of June 27, 2006 is maintained for claims 1-5, 7-12, and 41-43, and is further applied to newly added claim 55 for the reasons of record.

Applicants disagree with the rejections, arguing that the claimed invention has a specific and substantial utility and that one of ordinary skill in the art would find the specific and substantial utility to be credible, citing various sections of MPEP directed to utility requirements of 35 U.S.C. §§ 101 and 112, first paragraph. Applicants state that the specification teaches that the new FGF polypeptides disclosed in the application share sequence similarity with other members of the FGF family, the new murine FGF protein disclosed in the application is most closely related to FGF-4, FGF-6, and FGF-15, the new FGF disclosed in the application is expressed primarily in the liver, and the new FGF polypeptides disclosed in the application are secreted into the bloodstream where they would be expected to exert effects on distal sites, additionally teaching a specific phenotype expressed by transgenic mice expressing an FGF transgene of the invention; and that the new FGF molecules can be used to regulate growth, differentiation, and stimulation of cells within or near the liver, or as growth or fat deposition

inhibitors, or in the treatment or diagnosis of liver-related diseases and disorders. Applicant's arguments have been fully considered but are not found persuasive.

It should be noted that the instant claims and the instant specification identify SEQ ID NOS: 1, 2, 3, 4, 5 and 6 as nucleic acids and polypeptides encoding FGF-like polypeptides (emphasis added). Thus, their establishment as new FGF polypeptides remains to be elucidated, and further constitutes the grounds for the instant rejections. The specification teaches that the "FGF-like" polypeptide is structurally similar to known members of the fibroblast growth factor (FGF) family, with the highest sequence identity being 32% identity to FGF-6 and 28% identity to FGF-4 for the murine FGF-like protein SEQ ID NO: 4 (p. 19), and appears to contain a signal peptide indicating that it is a secreted protein. Therefore, even at the polypeptide level, the degree of homology to known FGF members is not substantial, and further, the putative signal peptide remains to be confirmed in function. Thus, any secretion of the polypeptides into the bloodstream is based on conjecture. Moreover, the specification does not describe how the FGF-like protein might "stimulate" or "regulate" these tissues, what it would stimulate them to do or what process it would regulate or in which way, or what the consequence of exposure to exogenous FGF-like protein would be. With respect to stimulating liver cells, this purported function is at odds with the results obtained with the transgenic mice that ectopically over-express the FGF-like polypeptide, since they had an underdeveloped or underweight liver. Thus it is left to one of skill in the art to determine which of these possible activities, if any, the FGF-like polypeptide may exert and the nature or outcome of such activities or use as a therapeutic composition. The specification merely invites one of skill in the art to determine if the FGF-like polypeptide stimulates any of these tissues and in what way, and to determine if the FGF-like polypeptide regulates a process in these tissues, what process, and in which way it regulates it.

Regarding Applicants' arguments that the new FGF molecules can be used in the treatment or diagnosis of liver-related diseases, or disorders, the specification speculates that the FGF-polypeptide or the nucleic acid encoding it "may" be useful as an inhibitor of growth or fat deposition or "may" be useful in the treatment of diagnosis of a medical condition such as cirrhosis or other toxic insult of the liver; inflammatory bowel disease, mucositis, Crohn's disease, or other gastrointestinal abnormality; diabetes; neurodegenerative diseases; wounds; damage to the corneal epithelium, lens, or retinal tissue, damage to renal tubules as a result of

acute tubular necrosis; hematopoietic cell reconstitution following chemotherapy; multiple sclerosis; alopecia; diseases or abnormalities of androgen target organs; infantile respiratory distress syndrome, bronchopulmonary dysplasia, acute respiratory distress syndrome, or other lung abnormalities; or tumors of the eye or other tissues. The specification (p. 6) then contradictorily suggests that antibodies or other inhibitors of the binding of the FGF-like protein to its unknown receptor may be used to treat these same diseases. It is not reasonable that both the polypeptide and an inhibitor of the polypeptide or its expression would both be useful for treating the same medical condition. The specification does not explain how the FGF-like polypeptide, its coding nucleic acid, antibodies or inhibitors might be used to diagnose any of these conditions or diseases, i.e. it does not disclose whether an increased or decreased expression would be diagnostic or in which tissues or cells such diagnostic expression would occur. It is left to one of skill in the art to determine which, if any, of these diseases can be diagnosed or treated with any of the compounds relating to the FGF-like polypeptide described in the specification, and to devise how such diagnosis or treatment should be carried out.

Regarding Applicants' argument that the phenotype observed for a mouse that ectopically overexpressed the FGF-like polypeptide would somehow suggest to one of skill in the art that the polypeptide would be useful in affecting the weight of an animal, the observed phenotype of these mice was addressed in the previous rejection, as was the inadequacy of this evidence to convey a use that would provide immediate benefit to the public. These mice suffered from hypertrophy of several different organs, it is hardly surprising that they weighed less than normal age-matched mice. It is unclear how one of skill in the art could be expected to comprehend the specific and substantial use of a polypeptide that causes developmental organ abnormalities in mice when expressed inappropriately during development. Despite the liver hypertrophy of these mice, the specification suggests that the FGF-like polypeptide "may" "stimulate" liver tissue *inter alia*. This and other contradictions in the specification, such as the teaching that both the FGF-like polypeptide and its inhibitors would be useful for treating the same diseases, illustrate that the specification does not provide a specific and substantial use for the claimed invention but simply lists a variety of possible uses, in the hope that at least one of them might prove true.

As set forth in the previous rejection, the instant specification does not disclose a single specific and substantial use for the claimed invention that provides specific benefit in a currently

available form. Rather, the specification lists, for example, a variety of unrelated diseases that the instant invention "may" be useful in diagnosing or treating. Such disclosure is nothing more than an invitation to one of skill in the art to go out and determine for which, if any, of these diseases the claimed invention might be useful in diagnosing or treating. The specification merely provides an invitation to those of skill in the art to determine biochemical and physiological functions of these products, and devise assays for those functions.

Applicants have provided a Declaration by Dr. Ornitz under 37 C.F.R. § 1.132, stating that the sequence of the new FGF disclosed in the application is more like other FGFs than any other molecule, and second, that the conserved FGF core domain, which is found in all FGFs, is present in the new FGF disclosed in the application, concluding that the new FGF disclosed in the application is in fact a member of the FGF family of proteins. Dr. Ornitz also states that after reading the application, he recognized that the new human and murine FGFs disclosed in the application are orthologs, and that the specification shows that the genes encoding these new FGFs are both strongly expressed in the liver, an expression pattern unknown for any other FGF.

In response, it is noted that the activity of the mouse and human polypeptides remains unknown. Further, conserved FGF core sequences *per se* do not provide any insight into the activity of the proteins, especially in the absence of any structure/function relationship and whether said core sequences are similarly located to a folded FGF protein, especially given the low percentage homologies for the overall sequence, as indicated in the foregoing.

Moreover, as previously disclosed, it was recognized in the art that FGFs are members of a protein family which has demonstrated a broad range of biological activities involving cell proliferation and differentiation during embryogenesis and post-natally and tissue maintenance, but that individual members of the FGF family have distinct functions and activities, i.e. one member of the FGF family cannot, in general, substitute for another member. While there is some overlap in function or activity between individual members, their range of function precludes *a priori* determination of the function of a newly discovered member of the family, such as the FGF-like polypeptides of SEQ ID NOs: 2 and 4. Galzie et al. (Biochem. Cell Biol. 75: 669-685, 1997), discloses that the FGF family is complex and diverse (see abstract). Table 1 of Galzie et al. details the biological significance of the first 9 members of this protein family, wherein none of the associated functions are found in common with any other family member.

The family is named after the initial discovery of FGF1 and FGF2, which are mitogenic for fibroblasts. However, some FGF members are not mitogenic for fibroblasts. For example, FGF-7 is secreted by fibroblasts, but is mitogenic for epithelial cells (page 671, col. 2). Goldfarb (Cytokine & Growth Factor Rev. 7(4): 311-325, 1996) teaches that the members of the FGF family mediate diverse response during embryogenic, fetal and postnatal development in complex interactions between other FGF members and other non-FGF regulatory molecules. The various FGF members bind to one or more of seven different FGF receptors (FGFR), and the expression of the FGF members and the receptors are strictly regulated both spatially and temporally during development. Different FGFs and FGFRs are involved in different processes during development, in some cases cooperatively and sometimes antagonistically. The effect of exposing a given cell type to a specific FGF depends on the cell type and what FGFRs it is expressing at the time of exposure. In an experiment similar to that described in the instant specification, Hu et al. (Mol. Cell. Biol. 18(10): 6063-6074, Oct. 1998) describe transgenic mice that ectopically overexpress FGF-18 under control of a liver specific promoter. The native FGF-18 gene was found to be expresses primarily in lung and kidney, and little or not at all in liver. The resulting mice had increased liver and small intestine mass as a fraction of body weight, and FGF-18 was found to induce proliferation of a variety of specific cells of epithelial and mesenchymal origin. These results show that the tissue that predominately expresses an FGF member may not be the tissue that responds to the FGF. In contrast to these results, ectopic expression of the instant FGF-like polypeptide in transgenic mice resulted liver hypotrophy, not hypertrophy, as one would expect if the polypeptide promoted proliferation of liver cells, as suggested in the specification. Thus, the suggestion is that the FGF-like polypeptide of the invention might have an activity or use shared with another member of the FGF family, but without any experimental evidence to show that the FGF-like polypeptide in fact possessed any activity or use in common with any of the other FGF members, or if so, what that activity or use was or might be.

Regarding Applicants' assertion that the genes encoding these new FGFs are both strongly expressed in the liver, an expression pattern unknown for any other FGF, it is noted that Nishimura et al. (of record) identified FGF-21, as a gene most abundantly expressed in the liver.

Regarding the observations from ectopic expression of FGF-like polypeptide in transgenic mice, Dr. Ornitz states that the specification identifies a phenotype that appears to result from transgenic overexpression of the new FGF disclosed in the application in multiple lines of mice. However, such an observation provides little insight for the actual function or use of the polypeptide, as indicated above.

Applicants next refer to Dr. Ornitz' assertion that new FGF disclosed in the application could be used, in one example, as a diagnostic molecule for assessing liver function, as new human and murine FGFs disclosed in the application were strongly expressed in liver, would be typically secreted, and possessed sequences that are unique enough to permit the isolation of monoclonal or polyclonal antibodies for use in detecting the presence of the new FGF in the bloodstream, bile, or other bodily fluids. Concluding that in view of Dr. Ornitz' statements, Applicants' specification sets forth at least one reasonable and beneficial use for the claimed invention, and that any reasonable use can be viewed as providing a public benefit and should be accepted as sufficient, at least with regard to defining a substantial utility.

Such is not found persuasive, because, the issue is not whether the FGF-like molecules could be detected, but whether their detection would be diagnostic for any given disease, condition or abnormality. Applicants have not provided a nexus between the unknown function of the FGF-like molecules and any disease or abnormality. Liver expression *per se* does not provide for a function for the instantly claimed polypeptides. Furthermore, a person of ordinary skill in the art would not know how to use such information in the absence of known function or correlation with a given disease state. This is additionally applicable to the assertion in the Declaration that because FGF2 and FGF7 were being evaluated for therapeutic use, it would be reasonable to believe that the new FGF could also be used therapeutically.

Such is not found persuasive, because an evaluation of other known FGFs for therapeutic use does not indicate the establishment of such use. Further, there is no teaching in the instant specification for any function for the FGF-like polypeptides, let alone any similarities to the functions of FGF2 and FGF7, especially in light of the diverse physiological effects exhibited by different members of the FGF family. Thus, the conclusion that the new FGFs would be expected to be secreted into the bloodstream and expected to have the properties of other FGFs, including affecting cell regulation, differentiation and physiology, is premature and based on

conjecture. Furthermore, even if the FGF-like molecules inherently possess the properties and activities of other FGFs, a person of ordinary skill would not know what such properties or activities are, or how they may be utilized, without further undue experimentation.

As stated in MPEP 2138.05-VIII, A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." *Bindra v. Kelly*, 206 USPQ570, 575 (Bd. Pat. Inter. 1979). Furthermore, as stated in MPEP 2107.01, situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities".

With regard to Dr. Ornitz statement that it is not surprising that one property of this new FGF is to inhibit growth or metabolic activity and thus cause weight loss in transgenic mice expressing the FGF, it should be noted that the transgenic mice were observed to have underdeveloped or underweight livers. As the observed phenotype appears to be at odds with the high expression of the FGF-like polypeptides in normal liver, no conclusions may be drawn as to the function of the polypeptides.

The instant specification provides no more than suggestions for various avenues of experimental investigation to determine what biological or pharmacological activities the FGF-like polypeptide might have and what practical use the nucleic acids, polypeptides, antibodies, etc. may be derived from such activities. A "patent is not a hunting license. It is not the reward for the search, but compensation for its successful conclusion," *Brenner* at 696 and *Kirk* at 53. *In re Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct, 1966) and *In re Kirk*, 153 USPQ 48 (CCPA 1967). Applicants should also note "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

Thus, the rejection of claims 1-5, 7-12, and 41-43 is maintained and is further applied to newly added claim 55 for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 102

Claims 1, 2, 4, 8, 9, 11, 39 and 49-51 were rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Acc. No. AQ175436, 10/17/98, as evidenced by Kennel, D.E. (Progr.

Nucl. Acid Res. Mol. Biol. 11: 259-301, 1971); claims 1 and 39 were rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Acc. No. AV050323, 6/22/99, as evidenced by Kennel, D.E. (Progr. Nucl. Acid Res. Mol. Biol. 11: 259-301, 1971); claims 2, 4, 8, 9, and 11, 49, 50, and 51 were rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over GenBank Acc. No. AV050323, 6/22/99, as evidenced by Kennel, D.E. (Progr. Nucl. Acid Res. Mol. Biol. 11: 259-301, 1971); and claims 1-4, 8-11, 13, 39, 41, 49-52 were rejected under 35 U.S.C. 102(e) as being anticipated by Edwards et al., US 6,639,063), in the previous office action dated June 27, 2006. The cancellation of claims 13, 39 and 49-52 renders their rejections moot. In view of Applicants' cancellation of subpart (d) of claim 1, removing language directed to hybridization of the claimed sequences, and thus obviating the grounds of rejection, the previous rejections are hereby withdrawn.

Conclusion

Claims 1-5, 7-12, 41-43 and 55 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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